Facile access to 3,5-symmetrically disubstituted 1,2,4-thiadiazoles through phosphovanadomolybdic acids catalyzed aerobic oxidative dimerization of primary thioamides

Kazuhisa Yajima, Kazuya Yamaguchi, and Noritaka Mizuno*
Department of Applied Chemistry, School of Engineering, The University of Tokyo, 7-3-1 Hongo, Bunkyo-ku, Tokyo 113-8656, Japan.
E-mail: tmizuno@mail.ecc.u-tokyo.ac.jp

Experimental details

**General:** HPLC analyses were performed on Shimadzu Prominence system with a UV detector (Shimadzu SPD-20A, 254 nm) equipped with a Shiseido CAPCELL PAK UG80 column (4.6 mm ID × 250 mm length) using a mixture of acetonitrile/water as an eluent (9/1 v/v). GC analyses were performed on Shimadzu GC-2014 with a FID detector equipped with an InertCap 1 capillary column. GCMS spectra were recorded on Shimadzu GCMS-QP2010 at an ionization voltage of 70 eV equipped with an InertCap 5MS/Sil capillary column. Liquid state $^1$H and $^{13}$C NMR spectra were recorded on JEOL ECA-500. $^1$H and $^{13}$C NMR spectra were measured at 500 and 125 MHz, respectively, with TMS as an internal standard ($\delta = 0$ ppm). H$_3$PW$_{12}$O$_{40}$, H$_4$SiW$_{12}$O$_{40}$, and PMo$_{12}$O$_{40}$ were obtained from Wako, and other heteropoly acids were obtained from Nippon Inorganic Colour & Chemical (the numbers of water of crystallization were 20–30 per polyanion). Solvents and substrates were obtained from Kanto Chemical, TCI, Wako, or Aldrich (reagent grade), and used as received.

**Procedure for oxidative dimerization:** 1 (0.5 mmol), H$_6$PV$_3$Mo$_9$O$_{40}$ (5 mol%), naphthalene (0.1 mmol, internal standard), and ethanol (4 mL) were placed in a Pyrex-glass tube reactor with a magnetic stir bar, and the reaction was carried out at 30 °C in 1 atm of O$_2$. The color of the reaction solution immediately after beginning was dark green for aromatic and heterocyclic thioamides (dark blue color of reduced H$_6$PV$_3$Mo$_9$O$_{40}$ + yellow color of thioamides) or dark blue (dark blue color of reduced H$_6$PV$_3$Mo$_9$O$_{40}$) and gradually changed to orange-yellow with the formation of elemental sulfur according to the consumption of 1 (Fig. S1). During the reaction, the conversion of 1 and the yield of 2 (based on 1) were periodically monitored by HPLC analysis. The typical HPLC charts are shown in Fig. S3. With regard to aliphatic thioamides, the conversion of 1 and the yield of 2 were periodically monitored by GC analysis.

As for product isolation, naphthalene was not used. For the isolation of 2a–2d, the reactions were carried out in acetonitrile. For other thiazoles, the reactions were carried out in ethanol. After complete conversion of 1, n-hexane (25 mL) and water (25 mL) were added
to the reaction mixture (without removal of elemental sulfur), followed by extraction with 
$n$-hexane ($25 \text{ mL} \times 3$) to afford 2. All products were confirmed by their MS and NMR data, 
and the data are summarized below.

**Compound data**

**3,5-Diphenyl-1,2,4-thiadiazole (2a):** As for isolation, the reaction was carried out in 
acetonitrile for 2 h. Melting point: 88.0–88.5 °C. MS (EI) $m/z$ (%): 238 (37) [$M^+ 135$ (100), 
103 (18), 77 (19). $^1$H NMR (500 MHz, CDCl$_3$, TMS): $\delta$ 8.39–8.41 (m, 2H), 8.05–8.07 (m, 
2H), 7.50–7.55 (m, 6H). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$, TMS): $\delta$ 188.1, 173.8, 132.9, 
131.9, 130.7, 130.3, 129.3, 128.7, 128.3, 127.5.

**3,5-Bis(4-methoxyphenyl)-1,2,4-thiadiazole (2b):** As for isolation, the reaction was carried 
out in acetonitrile for 2 h. Melting point: 138.5–139.0 °C. MS (EI) $m/z$ (%): 299 (11), 298 (53) 
[$M^+ 166$ (11), 165 (100), 150 (26), 133 (41), 103 (11), 90 (12). $^1$H NMR (500 MHz, CDCl$_3$, 
TMS): $\delta$ 8.31–8.33 (m, 2H), 7.98–8.00 (m, 2H), 7.00–7.02 (m, 4H), 3.894 (s, 1H), 3.885 (s, 
1H). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$, TMS): $\delta$ 187.4, 173.4, 162.5, 161.3, 129.9, 129.2, 
126.0, 123.7, 114.5, 114.0, 55.5, 55.4.

**3,5-Bis(4-chlorophenyl)-1,2,4-thiadiazole (2c):** As for isolation, the reaction was carried 
out in acetonitrile for 6 h. Melting point: 145.0–146.0 °C. MS (EI) $m/z$ (%): 308 (20), 306 (28), 
171 (38), 169 (100), 102 (13), 75 (12). $^1$H NMR (500 MHz, CDCl$_3$, TMS): $\delta$ 8.31–8.33 (m, 
2H), 7.98–7.99 (m, 2H), 7.47–7.52 (m, 4H). $^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$, TMS): $\delta$ 
187.1, 172.8, 138.2, 136.6, 131.2, 129.7, 129.6, 129.0, 128.7.

**3,5-Bis(4-trifluoromethylphenyl)-1,2,4-thiadiazole (2d):** As for isolation, the reaction was 
carried out in acetonitrile for 2 h. Melting point: 98.5–99.0 °C. MS (EI) $m/z$ (%): 374 (25) 
[$M^+ 204$ (10), 203 (100), 145 (12), 77 (19). $^1$H NMR (500 MHz, CDCl$_3$, TMS): $\delta$ 8.51 (d, 
$J = 8.0$ Hz, 2H), 8.18 (d, $J = 8.0$ Hz, 2H), 7.81 (d, $J = 8.0$ Hz, 2H), 7.78 (d, $J = 8.0$ Hz, 2H). 
$^{13}$C{$^1$H} NMR (125 MHz, CDCl$_3$, TMS): $\delta$ 187.0, 172.8, 138.1, 136.5, 131.1, 129.6, 128.9, 
128.6, 128.2.
3,5-Bis(furan-2-yl)-1,2,4-thiadiazole (2e): As for isolation, the reaction was carried out in ethanol for 2 h. Melting point: 101.5–102.0 ºC. MS (EI) m/z (%): 219 (10), 218 (76) [M⁺], 125 (100), 97 (10), 93 (14), 70 (10). ¹H NMR (500 MHz, CDCl₃, TMS): δ 7.64 (dd, J = 2.0, 0.5 Hz, 1H), 7.61 (dd, J = 2.0, 0.5 Hz, 1H), 7.29 (dd, J = 3.5, 0.5 Hz, 1H), 7.23 (dd, J = 3.5, 0.5 Hz, 1H), 6.64 (dd, J = 3.5, 2.0 Hz, 1H), 6.57 (dd, J = 3.5, 2.0 Hz, 1H). ¹³C{¹H} NMR (125 MHz, CDCl₃, TMS): δ 177.0, 164.9, 148.1, 146.5, 145.6, 144.5, 112.71, 112.68, 112.6, 111.8.

3,5-Bis(thiophen-2-yl)-1,2,4-thiadiazole (2f): As for isolation, the reaction was carried out in ethanol for 2 h. Melting point: 90.0–91.0 ºC. MS (EI): m/z (%): 250 (51) [M⁺], 141 (100), 109 (24). ¹H NMR (500 MHz, CDCl₃, TMS): δ 7.93 (dd, J = 3.5, 1.0 Hz, 1H), 7.70 (dd, J = 3.5, 1.0 Hz, 1H), 7.59 (dd, J = 5.0, 1.0 Hz, 1H), 7.46 (dd, J = 5.0, 1.0 Hz, 1H), 7.17 (dd, J = 5.0, 3.5 Hz, 1H), 7.15 (dd, J = 5.0, 3.5 Hz, 1H). ¹³C{¹H} NMR (125 MHz, CDCl₃, TMS): δ 180.7, 168.4, 136.2, 133.1, 130.6, 129.9, 129.2, 128.8, 128.4, 127.9.

3,5-Dimethyl-1,2,4-thiadiazole (2g): MS (EI) m/z (%): 114 (38) [M⁺], 73 (100). The reaction was carried out in CD₃OD, and the NMR spectra of the filtrate were measured after the reaction. ¹H NMR (500 MHz, CD₃OD, TMS): δ 2.79 (s, 3H), 2.58 (s, 3H). ¹³C{¹H} NMR (125 MHz, CD₃OD, TMS): δ 189.1, 174.1, 18.3, 16.4.

3,5-Diethyl-1,2,4-thiadiazole (2h): MS (EI) m/z (%): 142 (35) [M⁺], 87 (100), 86 (24), 59 (10). The reaction was carried out in CD₃OD, and the NMR spectra of the filtrate were measured after the reaction. ¹H NMR (500 MHz, CD₃OD, TMS): δ 3.14 (q, J = 7.5 Hz, 2H), 2.94 (q, J = 7.5 Hz, 2H), 1.41 (t, J = 7.5 Hz, 3H), 1.34 (t, J = 7.5 Hz, 3H). ¹³C{¹H} NMR (125 MHz, CD₃OD, TMS): δ 195.6, 179.3, 27.0, 25.5, 13.8, 12.6.
MS spectra
MS spectra
$^1$H NMR spectrum of 2a

CDCl$_3$

$X$: parts per Million: Proton
$^{13}$C NMR spectrum of 2a
$^{13}$C NMR spectrum of 2b

\[ \text{CDCl}_3 \]
$^1$H NMR spectrum of 2d

X: parts per Million : Proton

CDCl$_3$
\( ^1\text{H} \) NMR spectrum of 2f

\[ \text{X : parts per Million : Proton} \]

\[ X \colon \text{parts per Million : Proton} \]

\[ X \colon \text{parts per Million : Proton} \]
Table S1 Comparison of the present phosphovanadomolybdic acids catalyzed system with previously reported ones (for dimerization of 1a to 2a)

<table>
<thead>
<tr>
<th>Catalyst</th>
<th>Oxidant</th>
<th>Additive</th>
<th>Solvent</th>
<th>Temp.(°C)</th>
<th>Time</th>
<th>Yield (%)</th>
<th>TON</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>H₄PV₃Mo₉O₄₀ (0.4 mol%)</td>
<td>O₂ (1 atm)</td>
<td>—</td>
<td>EtOH</td>
<td>30</td>
<td>5 h</td>
<td>93</td>
<td>233 (Fig. 1, entry 2)</td>
<td>This work</td>
</tr>
<tr>
<td>—</td>
<td>Ar₂SeO (1.2 equiv.)</td>
<td>—</td>
<td>AcOH</td>
<td>75</td>
<td>24 h</td>
<td>84</td>
<td>Stoichiometric</td>
<td>6</td>
</tr>
<tr>
<td>—</td>
<td>Ar₂TeO (1.2 equiv.)</td>
<td>—</td>
<td>AcOH</td>
<td>RT</td>
<td>12 h</td>
<td>53</td>
<td>Stoichiometric</td>
<td>6</td>
</tr>
<tr>
<td>—</td>
<td>PhTeOSO₂CF₃ (1 equiv.)</td>
<td>—</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>0.5 h</td>
<td>71</td>
<td>Stoichiometric</td>
<td>7</td>
</tr>
<tr>
<td>—</td>
<td>Iodobenzene diacetate (1 equiv.)</td>
<td>—</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>3 min</td>
<td>95</td>
<td>Stoichiometric</td>
<td>8a</td>
</tr>
<tr>
<td>—</td>
<td>Iodobenzene diacetate (1 equiv.)</td>
<td>—</td>
<td>1-n-butylpyridinium tetrafluoroborate</td>
<td>75</td>
<td>15 min</td>
<td>91</td>
<td>Stoichiometric</td>
<td>8b</td>
</tr>
<tr>
<td>—</td>
<td>λ³-Iodane (1 equiv.)</td>
<td>—</td>
<td>CH₃CN</td>
<td>Reflux</td>
<td>1 h</td>
<td>82</td>
<td>Stoichiometric</td>
<td>8c</td>
</tr>
<tr>
<td>—</td>
<td>α-iodoxybenzoic acid (1.1 equiv.)</td>
<td>Et₄NBr (1.1 eq.)</td>
<td>CH₃CN</td>
<td>RT</td>
<td>5 min</td>
<td>95</td>
<td>Stoichiometric</td>
<td>8d</td>
</tr>
<tr>
<td>—</td>
<td>Pentylypyridinium tribromide (1 equiv., prepared from pentylypyridinium bromide and Br₂)</td>
<td>—</td>
<td>—</td>
<td>RT</td>
<td>4 min</td>
<td>97</td>
<td>Stoichiometric</td>
<td>9</td>
</tr>
<tr>
<td>—</td>
<td>2,3-Dicyano-5,6-dichloro-1,4-benzoquinone (1 equiv.)</td>
<td>—</td>
<td>CICH₂CH₂Cl</td>
<td>RT</td>
<td>&lt;5 min</td>
<td>95</td>
<td>Stoichiometric</td>
<td>10</td>
</tr>
<tr>
<td>—</td>
<td>N-bromosuccinimide (1.05 equiv.)</td>
<td>A₁₂O₃ (500 mg)</td>
<td>—</td>
<td>RT</td>
<td>5 min</td>
<td>92</td>
<td>Stoichiometric</td>
<td>11</td>
</tr>
<tr>
<td>—</td>
<td>DMSO (large excess)</td>
<td>1-Methyl-2-chloropyridinium iodide (0.03 equiv.)</td>
<td>DMSO</td>
<td>60</td>
<td>2.5 h</td>
<td>&gt;99</td>
<td>Stoichiometric</td>
<td>12a</td>
</tr>
<tr>
<td>Catalyst</td>
<td>Oxidant</td>
<td>Additive</td>
<td>Solvent</td>
<td>Temp.(°C)</td>
<td>Time</td>
<td>Yield (%)</td>
<td>TON</td>
<td>Ref.</td>
</tr>
<tr>
<td>----------</td>
<td>---------</td>
<td>----------</td>
<td>-------------</td>
<td>-----------</td>
<td>-------</td>
<td>-----------</td>
<td>----------</td>
<td>-------</td>
</tr>
<tr>
<td>—</td>
<td>DMSO (1 equiv.)</td>
<td>2-chloro-1,3-dimethylimidazolinium chloride (1 equiv.)</td>
<td>CH₂Cl₂</td>
<td>RT</td>
<td>26 h</td>
<td>93</td>
<td>Stoichiometric</td>
<td>12b</td>
</tr>
<tr>
<td>—</td>
<td>DMSO (1 equiv.)</td>
<td>2,4,6-trichloro-1,3,5-triazine (0.3 equiv.)</td>
<td>[bmim]BF₄</td>
<td>RT</td>
<td>10 min</td>
<td>96</td>
<td>Stoichiometric</td>
<td>12c</td>
</tr>
<tr>
<td>—</td>
<td>DMSO (large excess)</td>
<td>HCl (0.6 equiv.)</td>
<td>DMSO</td>
<td>35</td>
<td>3 h</td>
<td>&gt;99</td>
<td>Stoichiometric</td>
<td>12d</td>
</tr>
<tr>
<td>CuBr (10 mol%)</td>
<td>TBHP (1.4 equiv.)</td>
<td>—</td>
<td>CICH₂CH₂Cl</td>
<td>RT</td>
<td>0.5 h</td>
<td>79</td>
<td>7.9</td>
<td>13</td>
</tr>
<tr>
<td>Eosin Y (2 mol%)</td>
<td>Air (1 atm)</td>
<td>Photoirradiation (18 W fluorescent lamp)</td>
<td>DMF</td>
<td>RT</td>
<td>4 h</td>
<td>91</td>
<td>45.5</td>
<td>14</td>
</tr>
</tbody>
</table>
Fig. S1 Pictures of the reaction solution (a) immediately after beginning of the reaction and (b) at the end of the reaction (for the oxidative dimerization of 2g, see entry 8 in Fig. 1) and (c) elemental sulfur retrieved after the reaction. Elemental sulfur was retrieved by filtration and washed with ethanol and water (69 % yield with respect to 2g, 98.3 % purity by elemental analysis).
**Fig. S2** Reaction profiles for the H$_6$PV$_3$Mo$_9$O$_{40}$-catalyzed oxidative dimerization of 1a to 2a with or without a radical scavenger of 2,2,6,6-tetramethylpiperidine 1-oxyl (TEMPO). Reaction conditions: 1 (0.5 mmol), H$_6$PV$_3$Mo$_9$O$_{40}$ (1 mol%), TEMPO (0 or 0.5 mmol), ethanol (4 mL), O$_2$ (1 atm), 30 °C.
Fig. S3 HPLC charts for the H₆PV₃Mo₉O₄₀-catalyzed oxidative dimerization of 1a to 2a under the conditions described in Fig. S2. The asterisks indicate the signals due to H₆PV₃Mo₉O₄₀. Reaction conditions: 1 (0.5 mmol), H₆PV₃Mo₉O₄₀ (1 mol%), TEMPO (0 or 0.5 mmol), ethanol (4 mL), O₂ (1 atm), 30 °C.
**Scheme S1** Possible reaction mechanism (HPA = heteropoly acid, HPA_{red} = reduced heteropoly acid).